Subcutaneous adipose tissue exerts proinflammatory cytokines after minimal trauma in humans

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Pachler C, Ikeoka D, Plank J, Weinhandl H, Suppan M, Mader JK, Bodenlenz M, Regittnig W, Mangge H, Pieber TR, Ellmerer M. Subcutaneous adipose tissue exerts proinflammatory cytokines after minimal trauma in humans. Am J Physiol Endocrinol Metab 293: E690–E696, 2007. First published June 19, 2007; doi:10.1152/ajpendo.00034.2007.—Inflammatory cytokines released from adipose tissue play an important role in different pathological processes. In the present study, we investigated the inflammatory cytokine response of human subcutaneous adipose tissue (SAT) by applying the open-flow microperfusion technique. Four standard 18-gauge microperfusion catheters were inserted into periumbilical SAT of eight healthy male volunteers [29 ± 3 yr, BMI 24.3 ± 1.9 (mean ± SD)]. SAT probe effluents were collected at 60-min intervals for 8 h after catheter insertion. Different perfusion fluids were used to measure the local effect of insulin and/or glucose on the cytokine response. SAT probe effluents were analyzed for IL-1β, IL-6, CXCL8 (IL-8), and TNF-α. SAT concentrations of IL-1β increased 100-fold from 1.0 ± 0.2 pg/ml (mean ± SE) to 101.5 ± 23.2 pg/ml (P < 0.001) after 8 h. A 130-fold increase was observed for CXCL8, from 49 ± 29 to 6,554 ± 1,713 pg/ml (P < 0.001). Furthermore, a 20-fold increase of IL-6 was observed within the first 5 h (from 159 ± 123 to 3,554 ± 394 pg/ml; P < 0.001), and a significant decline to 2,154 ± 216 pg/ml (P < 0.01) was seen thereafter. Finally, TNF-α increased from 1.4 ± 0.6 to 2.5 ± 0.5 pg/ml (P < 0.05) in hour 2 and remained stable thereafter. Local administration of insulin exerted a stimulatory effect on the inflammatory response of IL-6. In conclusion, SAT exerts a highly reproducible and consistent proinflammatory cytokine response after minimally invasive trauma caused by the insertion of a catheter in humans.

open-flow microperfusion; interstitial fluid; acute inflammation

SUBCUTANEOUS ADIPOSE tissue, which originally was seen as a storage site for excessive lipids, has received increased attention as an important endocrine organ (12, 24). Several studies have shown that subcutaneous adipose tissue contributes to the production of a variety of biological mediators, such as adipokines (e.g., leptin, resistin, adiponectin) (25, 28, 36) and inflammatory cytokines (e.g., IL-1β, IL-6, CXCL8, IL-8, TNF-α) (9, 12, 18), that may play an important role in different physiological and pathophysiological processes. Recent studies have indicated that abundant adipose tissue depots contribute to the detrimental process of chronic low-grade inflammation by producing increased amounts of inflammatory cytokines and therefore link the pathogenesis of obesity, atherosclerosis, insulin resistance, diabetes, and their secondary disorders (9, 11, 31, 35). Hence it is of special interest to study adipocyto-
kines in vivo at the site of production to further elucidate the local role of these molecules in physiological processes as well as in diseases.

Besides adipocytes, the subcutaneous adipose layer contains connective tissue, nervous tissue, stromavascular cells, and immune cells. Together, these components function as an integrated unit. The in vivo investigation of this complex cell system and its mediators is of particular difficulty. It is likely that any trauma or foreign body introduced into the tissue (e.g., microdialysis or microperfusion catheters) will generate an immediate subsequent acute inflammation, which is a stereotypical response to recent or ongoing injury of vascularized living tissues (32). Because biological mediators, especially cell-to-cell communication molecules such as cytokines, are essential in triggering and perpetuating the process of inflammation (20, 32), the obvious question arises: how are these inflammatory cytokines generated and influenced by the trauma caused by the insertion of a catheter and the subsequent existence of a foreign body in the tissue? Therefore, the primary objective of the present study was to investigate the inflammatory response of subcutaneous adipose tissue after the insertion of a standard open-flow microperfusion catheter by measurement of the time profile of different inflammatory cytokines [IL-1β, IL-6, CXCL8, and TNF-α] in healthy volunteers.

Recent data from in vivo studies in humans applying hyperinsulinemic euglycemic clamp studies have produced evidence that cytokine release (IL-6 and TNF-α) could be influenced by insulin (14, 26). To further elucidate insulin’s role in modulating acute inflammation at the level of cytokines, our secondary objective was to investigate the effect of locally administered insulin on the proinflammatory cytokine response in subcutaneous adipose tissue.

METHODS

Subjects. This study was approved by the Ethical Committee of Medical University Graz and was performed in accordance with the guidelines proposed in the Declaration of Helsinki. All subjects were informed about possible risks and gave their written informed consent. Eight white male subjects, residents of the metropolitan area of Graz, Austria, participated in this study. Before the start of the study, all subjects were screened and information about their medical histories, physical examinations, and routine laboratory assessments were obtained. All subjects were healthy and were not taking any regular

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medication at the time of the study. The physical and biochemical characteristics of the subjects are shown in Table 1.

Open-flow microperfusion. Open-flow microperfusion is a validated technique to gain direct access to interstitial fluid in adipose and muscle tissue. The principle has been described in detail previously (2, 21, 23). For the present study, a conventional catheter (PEP Teflon 18-gauge Angiocath; Becton-Dickinson, Sandy, UT) was perforated with 100 holes (500 μm in diameter) with an excimer laser technique (LPX 205i; Lambda Physik, Gottingen, Germany). The catheter was inserted into the subcutaneous adipose tissue by using a steel mandrel. Afterward, the mandrel was replaced with two Teflon tubes (length, 6 mm and 56 mm; OD, 0.76 mm; ID, 0.3 mm; PTFE tubing; Cole Parmer, Vernon Hills, IL) connected to a screw cap. The systems were perfused at a flow rate of 1 μl/min by using a peristaltic pump (Minipuls 3; Gilson, Middleton, WI). Probe effluent samples were collected at 60-min intervals by using CMA Microvials (CMA/Microdialysis, Solna, Sweden). In the present study, four microperfusion catheters were placed in the periumbilical subcutaneous adipose tissue of each subject after local skin anesthesia by using 0.2 ml procaine hydrochloride without vasoconstrictor (Novanaest-purum; Gebro Pharma; Tyrol, Austria) to produce a superficial local skin welt. Catheters were placed at least 50 mm apart. Perfusion of the catheters was started immediately after catheter insertion.

Study protocol. Subjects arrived at the study center at 0700 after an overnight fast. Following a 15-min resting period, a venous cannula was inserted into a forearm vein and 30 ml of venous blood was withdrawn. The serum of this 30-ml sample from each subject was used to add endogenous albumin to the perfusate (see Perfusion fluid preparation). Additional samples were taken to quantify electrolytes; kidney, liver, and heart parameters; C-reactive protein; glucose; lipids; serum proteins; and blood count with technical differentiation (Table 2). Subsequently, the cannulated forearm was placed in a thermo-regulated box (≈55°C) to obtain arterialized blood samples during the study (17). Thereafter, the periumbilical skin of the abdomen was disinfected and local anesthesia was given by a physician who also inserted all four open-flow microperfusion catheters within 5 min. The study started (time 0) as soon as open-flow microperfusion effluent was collected from subcutaneous tissue. Probe effluent and corresponding blood samples were collected simultaneously at hourly intervals for the subsequent 8 h. To determine the flow rate of the catheters, CMA Microvials were weighed before and after sample collection. The weight difference was used to assess the volume, on average 66.9 ± 20.9 μl (mean ± SD), and to estimate the mean flow rate (1.12 ± 0.35 μl/min). Interstitial fluid and serum samples were stored immediately at −80°C. After two control samples were taken by using the same perfusate for all four subcutaneous adipose tissue catheters, the perfusates of catheters 2, 3, and 4 were changed to a perfusate containing insulin, glucose, and insulin + glucose, respectively (Fig. 1). During the whole study period, subjects rested in supine position and were allowed to drink water ad libitum but stayed otherwise in a fasting condition.

Perfusion fluid preparation. In total, four different perfusion fluids for the microperfusion catheters were prepared for each subject on the study day under aseptic conditions: 1) control (isotonic perfusate), 2) insulin (isotonic perfusate + 200 IU/l insulin; Actrapid; Novo Nordisk, Bagsværd, Denmark), 3) glucose (isotonic perfusate + 500 mg/dl glucose; 10% glucose; Fresenius Kab; Graz, Austria), and 4) insulin + glucose (isotonic perfusate + 200 IU/l insulin + 500 mg/dl glucose).

The isotonic perfusate consisted of ELO-MEL isoton (Fresenius Kab Austria; electrolyte composition in mmol/l: 140 Na+, 5 K+, 2.5 Ca2+, 1.5 Mg2+, and 108 Cl−). Twenty percent of serum from each subject was added to each homonymous perfusate bag to prevent nonspecific binding of insulin to the catheter system (2). To this perfusate, 250 mg/l inulin (Inutest; Laevosan, Linz, Austria) was added and was used to estimate the stability of the recovery of the catheter over time.

In vitro study. To validate the sampling of cytokines and to investigate the possibility of nonspecific binding of cytokines to the catheter and/or the tubing system, an in vitro study was performed. In brief, a catheter and tubing system similar to the system used during the study was perfused with isotonic perfusate containing cytokines at known concentrations. At fixed intervals, the solution passing through the system was collected and the cytokine concentrations were measured by using the same method. With the use of the above-mentioned isotonic solution, no relevant loss of cytokines due to nonspecific binding to the system was observed. Recovery rate of the expected concentration was 96.4 ± 6.5% (mean ± SD) for IL-1β, 92.8 ± 6.2% for IL-6, 99.9 ± 11.8% CXCL8, and 103.8 ± 5.8% for TNF-α.

Analytical procedures. IL-1β, IL-6, CXCL8, and TNF-α were determined by a multiplexed flow-cytometric assay using fluorokine MAP human base kit A, human IL-1β/IL-1F2 kit, human IL-6 kit, human IL-8 kit, and human TNF-α/TNFSF1AKit (R&D Systems, Minneapolis, Minn).

Table 1. Anthropometric and biochemical characteristics of study subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects, n = 8</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3 ± 1.9</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.87 ± 0.02</td>
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<tr>
<td>Fasting glucose, mg/dl</td>
<td>79.6 ± 8.4</td>
</tr>
<tr>
<td>Fasting insulin, μU/l</td>
<td>2.96 ± 1.24</td>
</tr>
<tr>
<td>Leukocytes, g/l</td>
<td>6.1 ± 1.8</td>
</tr>
<tr>
<td>C-reactive protein, mg/l&lt;sup&gt;+&lt;/sup&gt;</td>
<td>1.9 ± 1.4</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>140 ± 37</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>81 ± 37</td>
</tr>
</tbody>
</table>

Values are means ± SD. All subjects were male. *Normal range for C-reactive protein is defined as <8.0 mg/dl.

Table 2. Cytokines and their possible source cells in subcutaneous adipose tissue

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source, Example of Cells</th>
</tr>
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<tbody>
<tr>
<td>IL-1β</td>
<td>monocytes, macrophages, endothelial cells, dendritic cells, natural killer cells</td>
</tr>
<tr>
<td>IL-6</td>
<td>adipocytes, fibroblasts, endothelial cells, neutrophils, monocytes, macrophages, eosinophils, lymphocytes</td>
</tr>
<tr>
<td>CXCL8</td>
<td>monocytes, macrophages, lymphocytes, endothelial cells adipocytes, monocytes, macrophages, natural killer cells, lymphocytes, fibroblasts, endothelial cells</td>
</tr>
<tr>
<td>TNF-α</td>
<td>monocytes, macrophages, lymphocytes, endothelial cells adipocytes, monocytes, macrophages, natural killer cells, lymphocytes, fibroblasts, endothelial cells</td>
</tr>
</tbody>
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See Refs. 7, 10, 12, and 20.
Minneapolis, MN) on a Luminex 100 IS system (Luminex, Austin, TX). For IL-1β, the assay had a limit of detection of 0.27 pg/ml, an intra-assay coefficient of variation (CV) of 5.5%, and an interassay CV of 10.0%. For IL-6, the assay had a limit of detection of 0.36 pg/ml, an intra-assay CV of 5.2%, and an interassay CV of 10.1%. For CXCL8, the assay had a limit of detection of 0.39 pg/ml, an intra-assay CV of 7.8%, and an interassay CV of 18.7%. For TNF-α, the assay had a limit of detection of 0.47 pg/ml, an intra-assay CV of 4.3%, and an interassay CV of 10.7%. All samples from a subject were analyzed in duplicate on the same microtiter plate and during a single run of the system, to avoid interassay differences and to make a comparison between catheters or between interstitial fluid vs. serum concentrations more reliable. The inulin concentration in the probe effluent samples was measured photometrically with an adapted enzymatic kit (Gluco-quant; Roche Diagnostics, Mannheim, Germany) by using a standard laboratory analyzer (Cobas Mira; Hoffmann-La Roche, Basel, Switzerland). Insulin concentrations in the dialysate and serum were measured by using a commercial ultrasensitive insulin ELISA (10-1132-01; Mercodia, Uppsala, Sweden). Hourly measurements of glucose, lactate, pH, PO2, PCO2, Na⁺, K⁺, and hematocrit were performed by using a standard blood gas analyzer (Roche OMNI S6; Roche Diagnostics). On the morning of the screening visit and the study day, blood count with technical differentiation; electrolytes; kidney, liver, and heart parameters; C-reactive protein; glucose; lipids; and serum proteins were measured by using conventional laboratory methods. To ensure that no relevant amount of cytokines was delivered to the tissue by the perfusate (containing 20% of serum), cytokine concentrations were measured in all perfusion fluids.

Statistical analysis. Unless otherwise indicated, results in the text, figures, and tables are presented as means ± SE. Analysis of cytokine trends within catheters were made by using a Student’s paired t-test (on data normalized by logarithmic transformation as necessary). To investigate a local effect of insulin and/or glucose on adipose tissue cytokine release, the area under the curve (AUC) was calculated for each catheter from minute 180 to minute 480 (Fig. 1). AUC and individual time points were then compared between catheters with an unpaired Student’s t-test (on data normalized by logarithmic transformation as necessary). In all comparisons, a P value of <0.05 was considered significant. All analyses were performed by SPSS 13.0.1 for Windows (SPSS, Chicago, IL).

RESULTS

Serum cytokine concentrations. As expected, inflammatory cytokines were not detectable or close to the detection limit in serum in all subjects. IL-1β was detected in four out of eight subjects at low concentrations of 1.2 ± 0.4 pg/ml. IL-6 was detectable in five out of eight subjects at comparable concentrations to IL-1β of 2.1 ± 1.1 pg/ml. Serum concentrations of CXCL8 were not detectable, and TNF-α was detectable in seven out of eight study subjects at 1.9 ± 0.3 pg/ml. In general, serum cytokine concentrations were stable over time. No systemic increase of the concentrations was observed after insertion of open-flow microperfusion catheters.

Adipose tissue cytokine response to local trauma. Individual cytokine responses to the catheter were highly reproducible. Concentrations of IL-1β in the open-flow microperfusion probe effluent increased consistently from a starting value of 1.0 ± 0.2 pg/ml to a maximum at the end of the observed study period of 101.5 ± 23.2 pg/ml (P < 0.001, Fig. 2A). There was a precipitous increase of IL-6 from the starting value of 159 ± 123 pg/ml to a peak value in hour 5 of 3,554 ± 394 pg/ml (P < 0.001), and thereafter IL-6 declined significantly to a level of 2,154 ± 216 pg/ml (P < 0.01, Fig. 2B) at hour 8. CXCL8
showed a similar response compared with IL-1β, with a consistent increase from 49 ± 29 pg/ml to the end of the observed period, leveling at 6.554 ± 1.713 pg/ml (P < 0.001, Fig. 2C). In contrast to IL-1β, IL-6, and CXCL8, TNF-α increased significantly from the starting value of 1.4 ± 0.6 to 2.5 ± 0.5 pg/ml in the next sample (P < 0.05) and remained at slightly elevated levels for the remainder of the study period (Fig. 2D). Together, these results indicate a strictly individual but consistent and highly reproducible response of each investigated cytokine after catheter insertion that might reflect the individual functions of the investigated cytokines after acute trauma. Whereas a mild increase was observed for TNF-α, the response was 20-fold for IL-6, 100-fold IL-1β, and >130-fold for CXCL8.

Local effect of insulin and/or glucose on adipose tissue cytokine release. Time concentration profiles of individual cytokines after insertion of the catheter were also highly reproducible for catheters containing glucose, insulin, and glucose + insulin compared with the saline control catheter. Basal concentrations (minutes 60–120 after catheter insertion) were not different between groups. Whereas no effect of glucose was observed for any of the cytokines, a significant stimulatory effect of insulin on the inflammatory response of IL-6 was observed [AUC (180–480 min) control: 871 ± 73 ng·ml⁻¹·min; insulin: 1,595 ± 332 ng·ml⁻¹·min; P < 0.05]. Subsequent analysis of individual time points indicated significant differences (P < 0.05) between insulin and control catheter in hours 6, 7, and 8 (Fig. 3B). In support of this finding, a similar pattern was found for the glucose vs. insulin and glucose catheter (glucose: 956 ± 182 ng·ml⁻¹·min; insulin + glucose: 1,364 ± 359 ng·ml⁻¹·min), although this difference did not reach statistical significance. For all other cytokines, no significant effect of insulin was observed.

DISCUSSION

The present results revealed that subcutaneous adipose tissue exerts a reproducible and highly consistent proinflammatory response after minimal local trauma caused by the insertion of a catheter. The observed inflammatory response was distinctly different for various investigated cytokines in both magnitude and time pattern, suggesting a different physiological role of individual cytokines in response to local tissue trauma.

Inflammatory processes have been reported to start immediately after tissue damage (29, 32). In the present study, special care was taken to start sampling of interstitial fluid as soon as possible after catheter placement. Thus run-in phases or catheter equilibration periods, usually taken into account in microdialysis or microperfusion studies to restore tissue integrity, were avoided (2, 8). Also, it is important to note that the measured and reported concentrations do not represent the absolute concentration of the cytokines present in subcutaneous adipose tissue. With the use of open-flow microperfusion, factors such as catheter exchange area, perfusate, flow rate, and molecular weight of the substance of interest affect the equilibration between interstitial fluid and perfusate that is not complete with the used geometry and flow rate. Therefore, the measured concentration in the probe effluent represents only a fraction of the absolute interstitial fluid concentration. Previous studies applying the same technique have revealed recovery rates (or equilibration rates) for albumin and insulin using a...
flow rate of 0.5 μl/min of 20% (5) and 50% (2), respectively. Because the size of these proteins represent the range of the molecular weight of cytokines as investigated in the present study but a relatively higher flow rate of 1 μl/min was applied in the present study, the actual concentrations of the cytokines in the interstitial fluid surrounding the catheters can be expected to be ~5- to ~10-fold higher than the observed levels in the adipose tissue probe effluent. Inulin was used in the present investigation as an external recovery marker, and it indicated stable recoveries for the duration of the experiment. The magnitude of the cytokine response after catheter insertion varied substantially (from nearly 2-fold for TNF-α to >130-fold for CXCL8). Also, the time pattern was highly individual for each investigated cytokine (increase for IL-1β and CXCL8, increase/decrease for IL-6, increase/stable values for TNF-α). Therefore, it is highly likely that the observations in the present experiments are of a physiological nature rather than of methodological origin. Although IL-1β, IL-6, and CXCL8 concentrations measured in the first probe effluent sample were low compared with subsequent concentrations, they were already elevated compared with serum levels. This finding suggests that the investigated cytokines are produced in subcutaneous adipose tissue, by adipocytes themselves and/or inflammatory cells, infiltrated into the adipose tissue as a consequence of the local trauma. Several inflammatory and noninflammatory cells, which are already in the tissue or start to invade the affected area around the catheter, are likely to contribute to the production of locally released cytokines (Table 2). Specifically, macrophages and neutrophils, which are the predominant cells in the early phases of inflammation, could contribute to ignite the local production process (20, 32).

Sopasakis et al. (27), who measured interstitial IL-6 levels in abdominal and femoral adipose tissue by using microdialysis in 20 healthy volunteers, observed that the IL-6 levels tended to increase over the monitoring period. They speculated whether this increase might be due to a diurnal pattern of secretion, as seen for a variety of hormones, or whether it is caused by an inflammatory response of the tissue. The existence of a diurnal pattern of cytokine release also cannot be excluded from the present results. However, because no significant change was observed in the serum concentrations of the investigated cytokines, such an extraordinary high increase in subcutaneous adipose tissue cytokine concentrations is most likely explained by a local tissue response. In another study performed by Orban et al. (19), a standardized food intake was given 2 h after the insertion of subcutaneous microperfusion catheters. The investigators measured leptin, TNF-α, and IL-6 in the catheter effluents. They observed an increase in the effluent concentration of IL-6 during the postprandial period and suggested that this increase may be related to the food intake itself. A possible participation of a local inflammatory reaction was not considered by these authors. Particularly, because there was no control group in this study, it is likely that the conclusion that food intake stimulates IL-6 secretion was at least partially influenced by an overlapping inflammatory response.

In studies evaluating different technologies for continuous subcutaneous glucose monitoring, it is still heavily discussed how long it takes until “normal” physiological conditions are restored after catheter and/or sensor application (8, 34). In the present study, microperfusion was applied by using a standard 18-gauge cannula in subcutaneous adipose tissue of the periumbilical region, an insertion site that is preferably used also for the application of techniques for subcutaneous glucose monitoring (1, 3, 4, 15, 30). It is likely that, similar to the situation in this study, subcutaneous glucose sensors and microdialysis-based glucose monitoring techniques also cause an inflammatory response of the tissue. It was already hypothesized that an inflammatory process could be responsible for the often-observed lack of correlation between interstitial fluid glucose and blood glucose concentrations (8, 34).

Our present data suggest, for several cytokines, that basal conditions are not established, at least 8 h after induction of the local trauma. An interesting question remains: is this disturbance of cytokine levels only caused by the initial trauma of catheter insertion, or is it further augmented by the remaining foreign body of the catheter? The catheter used is made out of FEP-Teflon, a material extensively tested for its biocompatibility that has not been shown to provoke any significant inflammatory tissue reaction or foreign body granuloma formation in vivo (6, 16, 22). According to the literature, we hypothesize for the present investigation that the cytokine response is primarily initiated by the initial trauma caused by the catheter insertion.

As a secondary objective, we investigated whether elevated concentrations of insulin and/or glucose in the tissue surrounding the catheter might have an effect on cytokine concentrations measured in the probe effluent. The total administered amount of insulin was minimal (calculated by the difference between perfusate and probe effluent insulin concentration multiplied by the flow rate of the catheter and duration of the experiment); in fact, it was <30 mIU insulin (~15 mIU/catheter) for each subject. Because of the same inflow and outflow rates of the catheter, insulin was administered predominantly by passive diffusion. The intention was to substantially increase the insulin concentration in the direct vicinity (~1 mm) of the catheter but without a significant alteration in systemic insulin levels. Of course, limiting factors such as the small sample size (8 subjects) and the relatively high variability within the data have to be considered when interpreting the results. However, despite these limitations, insulin indicated a significant stimulating effect on IL-6 concentrations in the probe effluent from subcutaneous adipose tissue. The question of whether insulin has an effect on the IL-6 release has been addressed previously. Krogh-Madsen et al. (14) observed a stimulating effect of systemically elevated insulin on IL-6 mRNA expression in subcutaneous adipose tissue. This finding was confirmed by Westerbacka et al. (33) in 21 nondiabetic women, indicating that the stimulatory effect of hyperinsulinemia on IL-6 mRNA was even more pronounced in insulin-resistant women compared with insulin-sensitive controls. Soop et al. (26) demonstrated a significant additive effect of insulin on the IL-6 response in blood after endotoxin administration during a hyperinsulinemic euglycemic clamp vs. saline control experiments in healthy volunteers. In another model of low-dose endotoxemia in humans, Krogh-Madsen et al. (13) found increased IL-6 levels in blood during the late phase (180–360 min) of hyperinsulinemia induced either by a hyperglycemic or a hyperinsulinemic clamp. The methods used in these studies are substantially different from the present investigation. Also, it...
cannot be ruled out that insulin acts on a different mechanism after endotoxin has activated the systemic immune response of the body. However, present and previous results suggest that insulin has a stimulatory effect on the IL-6 release from subcutaneous adipose tissue.

In summary, our results demonstrate that after insertion of a microperfusion catheter, subcutaneous adipose tissue extracts a reproducible and highly consistent proinflammatory response of IL-1β, IL-6, CXCL8, and TNF-α. It can be concluded that the local inflammatory reaction due to insertion trauma results in a pathophysiological condition in the tissue surrounding the catheter. Therefore, our findings may have an important impact on the interpretation of previous studies using similar techniques that have addressed the investigation of adipose tissue physiology of small (e.g., glucose, lactate) and large (e.g., cytokines) compounds. On the other hand, the method of open-flow microperfusion will provide a novel in vivo model to further elaborate acute inflammation at the level of cytokines and to investigate the modulation of this response by the local delivery of active agents in humans.

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GRANTS

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